UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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MEETING

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THURSDAY,
JANUARY 13, 2005

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The Panel met at 9:00 a.m. in Salons A, B and C of the Hilton Washington, D.C., North/ Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Dr. William H. Maisel, Acting Chairperson, presiding.

PRESENT:

WILLIAM H. MAISEL, M.D.	Acting Chairperson
CHARLES R. BRIDGES, M.D.	Consultant
THOMAS B. FERGUSON, M.D.	Consultant
KENNETH W. JOHNSTON, M.D.	Consultant
JOANNE LINDENFELD, M.D.	Consultant
NORMAN S. KATO, M.D.	Consultant
MITCHELL W. KRUCOFF, M.D.	Member
MICHAEL C. MORTON	Industry Rep.
LINDA A. MOTTLE, M.S.M.R.N.,CCRP	Consumer Rep.
GARY G. NICHOLAS, M.D.	Consultant
SHARON-LISE T. NORMAND, Ph.D.	Member
JOHN C. SOMBERG, M.D.	Consultant
CLYDE YANCY, M.D.	Consultant
JUDAH Z. WEINBERGER, M.D., Ph.D.	Consultant
CHRISTOPHER J. WHITE, M.D.	Member
GERETTA WOOD	Exec. Secretary

FDA REPRESENTATIVES:

BRAM ZUCKERMAN, M.D.
DOROTHY ABEL
BINITA ASHAR, M.D., MBA
DAVID BUCKLES, Ph.D.
ANDREW FARB, M.D.
GARY L. KAMER
MEGAN MOYNAHAN

SPONSOR REPRESENTATIVES:

MICHEL S. MAKAROUN, M.D., F.A.C.S.
R. SCOTT MITCHELL, M.D., F.A.C.S.
MICHAEL C. NILSON

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P-R-O-C-E-E-D-I-N-G-S

9:01 a.m.

ACTING CHAIR MAISEL: Good morning. I would like to call to order this meeting of the Circulatory System Devices Panel. Today's topic is discussion of a pre-market application for the W.L. Gore and Associates GORE TAG Thoracic Endoprosthesis, P040043. I would like to ask Geretta Wood to read the Conflict of Interest statement.

EXEC. SEC. WOOD: The following announcement addresses Conflict of Interest issues associated with this meeting and is made a part of the record to prevent even the appearance of an impropriety. To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interest reported by the Committee participants. The Conflict of Interest statutes prohibit special Government employees from participating in matters that could affect their or their employer's financial interest.

However, the Agency has determined that participation of certain members and consultants, the

need for whose services outweighs the potential conflict of interest involved is in the best interest of the Government. Therefore, waivers have been granted for Drs. Charles Bridges, L. Henry Edmunds, Thomas Ferguson, William Maisel, Clyde Yancy and a waiver was previously granted for Dr. Judah Weinberger for their interest in firms that could potentially be affected by the Panel's recommendation.

The waivers for Drs. Bridges, Edmunds, Ferguson and Maisel involve a grant to their institution for the sponsor's study. The panelists had no knowledge of the funding and had no involvement in the generation or analysis. Dr. Ferguson's waiver also involves his affiliation with a nonprofit organization that is the recipient of an unrelated educational grant from a competitor.

Funding to the organization is between $100,001 and $300,000 per year. Dr. Yancy's waiver involves unrelated consulting services with a competitor for which his fees have not yet been determined. Dr. Weinberger's waiver includes a stockholding in a competitor in which the value is

between $50,001 and $100,000. The waivers allow these individuals to participate fully in today's deliberations.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 112A-15 of the Parklawn Building. We would like to note for the record that the Agency took into consideration other matters involving Drs. Mitchell Krucoff, Joanne Lindenfeld and Clyde Yancy. These panelists reported past or current interest involving firms at issue, but in matters that are not related to today's agenda. The Agency has determined therefore that these individuals may participate fully in the Panel's deliberations.

The Agency also would like to note that in the event that the discussion involves any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons

making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment on.

ACTING CHAIR MAISEL: Thank you, Geretta. My name is Dr. William Maisel. I'm a cardiologist at Brigham and Women's Hospital and I would like to invite the Panel Members to introduce themselves starting on my left with Dr. Zuckerman.

DR. ZUCKERMAN: Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. FERGUSON: Tom Ferguson, Professor Emeritus, Washington University, Saint Louis.

DR. LINDENFELD: Joanne Lindenfeld. I'm a Cardiologist at the University of Colorado.

DR. KRUCOFF: Mitch Krucoff. I'm a Cardiologist at Duke University Medical Center and the Director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute.

DR. NICHOLAS: Gary Nicholas, a vascular surgeon, Professor of Surgery, Penn State University, Lehigh Valley Hospital.

DR. BRIDGES: Charles Bridges,

Cardiothoracic Surgeon, University of Pennsylvania.

EXEC. SEC. WOOD: Geretta Wood, Executive Secretary for the Advisory Panel.

DR. SOMBERG: I'm John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago, Illinois.

DR. KATO: Norman Kato, Cardiothoracic Surgery, private practice, Encino, California.

DR. NORMAND: Sharon-Lise Norman, Professor of Health Care Policy and Biostatistics at Harvard Medical School and Harvard School of Public Health.

DR. JOHNSTON: Wayne Johnston, Vascular Surgeon, Professor of Surgery at University of Toronto.

DR. WEINBERGER: Judah Weinberger, Interventional Cardiologist at Columbia University.

MR. MORTON: Michael Morton. I'm the industry representative. I'm employed by Medtronics.

MS. MOTTLE: Linda Mottle, Director and Faculty of the Clinical Research Program at Gateway Community College.

ACTING CHAIR MAISEL: Thank you. Geretta, if you would read the voting status statement, please?

EXEC. SEC. WOOD: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for this meeting on January 13, 2005: Charles R. Bridges, M.D., L. Henry Edmunds, Jr., M.D., Thomas B. Ferguson, M.D., Kenneth W. Johnston, M.D., Joanne Lindenfeld, M.D., Norman S. Kato, M.D., Gary G. Nicholas, M.D., John C. Somberg, M.D., Clyde Yancy, M.D., Judah Z. Weinberger, M.D., Ph.D.

For the record, these individuals are special Government employees and are consultants to this Panel under the Medical Devices Advisory Committee. They have undergone the customary Conflict of Interest review and have reviewed the material to be considered at this meeting. The Agency would also like to note that Dr. William Maisel has consented to serve as Chair for the duration of this meeting. This

is signed by Daniel G. Schultz, M.D., Director, Center for Devices and Radiological Health and signed January 11, 2005.

ACTING CHAIR MAISEL: Thank you. Before we begin this morning's discussion on this application, the FDA has two brief presentations. I would like to invite Dr. Binita Ashar, Acting Clinical Director, of the CDRH to talk about the Critical Path Initiative.

DR. ASHAR: Great. Thank you and good morning. I appreciate this opportunity to discuss with you the Agency's Critical Path Initiative from the CDRH perspective. Basically, what I'm going to do this morning is I'm going to identify some of the challenges in medical product development. Then I will define for you what the Critical Path Initiative is and then describe what our future efforts are for bringing this initiative further.

Basically, the present state of affairs is that there is a scientific challenge that we have a number of disease processes, Alzheimer's, AIDS, cardiovascular diseases that need better treatments

and we not only need better treatments, but we need better preventative therapies. At the same time, we're faced with a societal challenge and that is the urgency for timely development of treatments for these diseases. And not only do we need these treatments to be timely, but we also need these treatments to be affordable.

In the present state of affairs, there is great optimism based on new biomedical discovery. We have sequenced the human genome. We have new genomic and proteomic technologies. There are advances in medical imaging. We have nanotechnology advances that potentially can offer the right treatment to the right patient in the right location with far fewer side effects than ever before. And at the same time, we have been investing to produce these basic biomedical advances.

There has been an increase in NIH funding of double over the past five years. And pharmaceutical research and development has also increased at the same rate. Overall, our society has provided major investments in basic biomedical

technology research and this is a graphical representation demonstrating the increase in research spending, both from the pharmaceutical RND side as well as in the NIH budget.

Now, you would expect that this acceleration in development, this would have translated into increased medical product development. However, from the drugs and biologic side, in fact, there has been a decline in the number of FDA new products that have been submitted. Now, this necessarily hasn't been the case for medical devices, but the fact of the matter is we could be doing better. And this is a graphical representation demonstrating the 10-year trend in pre-market device application showing the number of original PMAs that have been submitted.

Now, at the same time, we are noticing that, at least on the drug and biologic side, the cost of bringing a new drug to market is estimated to be about $1.7 billion, and the reason for this is largely because there is a high failure rate of new drug candidates late in the clinical development process.

Now, what is the cause of this problem? Well, some of these new technologies aren't at their full potential.

And what has been occurring or what we have noticed to occur is that industries have been focusing on easier targets and because of various business arrangements have focused on potentially the cash cows and not necessarily treatments that might affect smaller populations. They have found that the development process has become uncertain. Some of the additional challenges that I have mentioned already are that there is a failure late in the clinical development process, at least for drugs and biologics.

Now, I want to mention that the Critical Path is different for devices. Device development is different because of the device regulation process. We have a least burdensome provision of FDAMA, which is different than drugs and biologics. We are committed to finding a least burdensome path to market. We have quality systems and design controls that are not prescriptive, but are focused on what the end result is and has the product, indeed, met the expectations that we have requested.

The innovation process is different for devices. The small molecule issue is biocompatibility, not necessarily biometabolism. The process is an iterative process whereby sometimes during the clinical development phase, there might be minor changes in the device. There is a user learning curve that we face with the use of medical devices and performance and durability are also engineering issues. Different pharmaceuticals in the device industry is represented by small manufacturers that may not have the resources to put forth all of the time and effort and expenditures that they might need to to bring a product forward.

Other additional causative factors that have been shown as a hurdle in the medical product development is that some of the basic science investment and progress has surpassed what we are able to actually translate into new medical products. Essentially, we are using the evaluation tools and infrastructure of the last century to bring forth new medical products of this century. We are doing randomized controlled clinical trials like we have

always done them.

We are not necessarily using our cumulative knowledge of the society to overcome some of the development hurdles, so that we can bring medical products to market faster without compromising our safety and effectiveness evaluations. And this has resulted in a bottleneck at the Critical Path for delivering new medical products to patients.

So the central Critical Path thesis is that there has been a great societal investment in research and development to improve medical product development. However, there has not been an investment in the tools necessary to translate this basic biomedical research into new medical products. So what do I mean by this? Well, tools that might be computer simulation tools or registries or new surrogate markers that have been validated or biomarkers that might be able to identify patient populations that might be most amenable to these treatments that would potentially cut down the size of these various clinical trials.

There has been a great investment in the

basic research, but not investment and attention to the tools to bring this research to translate into medical products. And some of the problem is that academia is not adequately funded to perform the scientific investigations to develop new tools. This has generally not been conceptualized up until this point, at least, as being FDA's role. And any efforts to develop valuative tools in the private sector are proprietary and they are, therefore, not generalizable and available for use for the population at large.

So the FDA's Critical Path Initiative is an attempt to bring attention and focus to the need for targeted scientific efforts to modernize the techniques and methods used to evaluate the safety, effectiveness and quality of medical products as they move from product selection to design and mass manufacture. And this diagram demonstrates how Critical Path research differs from what is generally considered translational research.

You notice that basic scientific research is the type of research that is largely conducted by academic organizations and by our sister agencies like

NIH. NIH is also quite interested in translational research of bringing this new basic research into the clinical arena. However, Critical Path research is really FDA's arena where this translational research is looked at from the perspective of mass manufacture and mass marketing.

Can these clinical trial results formed in a small population translate into the generalized patient populations that we are approving a device for? And in evaluating any sort of medical products, you look at three dimensions of Critical Path. You look at safety. Can this device adequately perform in a safe manner? Can this device demonstrate efficacy in the population? And can this device be mass produced to the point that it is generalizable to not only the premiere centers in the United States, but also to all of the community hospitals? And can these results that we see in these early clinical trials be ones that can be replicated over and over again in smaller areas?

And so if we had tools that might be able to help us in our assessment in deciding whether a

product is safe or effective or can be industrialized, wouldn't it be great to be able to bring these products to development faster without compromising our safety and effectiveness evaluation? So basically, the Critical Path science basis is to be able to understand what types of tools we might be able to invest in.

And FDA potentially could take an organizational role in bringing groups together, consumer groups, patient groups, academia and industry groups to develop some of these scientific tools that might be then available in the public arena for use by all industry groups. And this is something that NIH and academia have generally not focused on and Critical Path is intended to be something that is supplementing what we already have learned in our translational research basis.

So the work ahead, basically, this is for scientific improvement. It is not to be confused with regulatory evolution or streamlining or making the paper pushing faster or easier. It is, essentially, using the science that we already know to develop

tools that help in our evaluations. The regulatory process is a related effort and can assist with this, but it is not the focus of this initiative.

So what have we done so far with Critical Path? Well, basically, there was a Federal Register docket open describing a Critical Path that was open through the summer and we received a number of responses from industry groups, patient groups, professional organizations, individual industries. This initiative was also presented to the FDA Advisory Board, the Science Board, to receive some of their feedback. And we have had individual meetings with various scientists, companies, patient groups and many, many others just to get the word out, just to get feedback out.

This has also been presented at the FDA Science Forum and at many speeches and panel presentations. And, basically, we have received overwhelming support. In fact, they have asked FDA to embark on doing things that is well outside of FDA's resources. And we have heard this really from all of our patient groups and all of our industry groups.

Submitters actually, again, ask for us to work on a number of things intent actually outside of some of our range. And some of the things that they suggested is, you know, streamlining clinical trials if we had better biomarkers, if we had a process by which we knew that we could validate a surrogate endpoint and promote effective product development. What they wanted repeatedly was FDA feedback on particular endpoints and particular surrogate endpoints. And how we can harmonize internationally so that we could better do this so that a clinical trial in one area of the world would be applicable to the United States, how we could focus on cancer trials, combination products.

Some industry groups actually have commented on the use of proprietary data. You know, very tentatively, they mentioned that perhaps FDA might find a way to use some of this information with the consent of all involved parties to further medical product development. And so, basically, the bottom line is this is an initiative that is intended to use science to integrate into the regulatory process, so

that we can make our safety and effectiveness evaluations faster and more cost effectively.

This is not just an FDA effort. We can't do this alone. We need to work with our stakeholders to make this a reality. And we need to focus on particular scientific areas that first and perhaps expand at a later date. So the next step on a Critical Path is from the docket we received a number of comments. We are identifying all of the possible proposals and prioritizing various opportunities for developing valuative tools. We will be putting forth a national Critical Path opportunities list that reflects all of the comments that we have received.

We need to find a mechanism by which we can continue to obtain such feedback and update this list so that not only FDA, but other interested parties, might embark on Critical Path research. Thank you very much for your attention.

ACTING CHAIR MAISEL: Thank you very much. Next, I would like to invite Megan Moynahan, who is the Branch Chief for Pacing, Defibrillator and Leads, to update the Panel on some recent decisions.

DR. MOYNAHAN: Good morning. Thank you very much. I would like to take a few minutes this morning to update you on the Panel meeting that occurred in July this past year in which the panelists discussed the Guidant Companion application, a labeling review, and the Philips Medical HeartStart Home Over-the-Counter AED.

Beginning with companion, the FDA raised a number of concerns to the Panel and I'm not going to represent them all here, but the primary one related to whether the Panel felt that the data were sufficient to support an expanded patient population for the Guidant CRT-D Device to include patients who did not have to have a requirement for an ICD. There was a lot of discussion about the change in definition of hospitalization and the FDA has some concern about how to interpret both the primary and secondary endpoints based on that.

We asked the Panel to comment on how the indication should be worded and we asked for some broad labeling recommendations on that application. The Panel recommended that the data supports expanding

the indicated patient population, but they had some concerns about how that would be worded in the indication statement. They specifically asked us to avoid using the term "all-cause hospitalization" in the indication statement. And they wanted a special separate section of the labeling to call out the benefit with respect to the primary endpoint.

The approved indications appears as follows, and as you see, it only indicates the intended patient population, so it is indicated for patients with moderate to severe heart failure who remain symptomatic despite stable optimal heart failure drug therapy and have an LVEF of less than 35 percent and a QRS no greater than 120. And now, there is a new clinical outcome section that appears in the labeling just after the indication statement in which we go into more detail as to the clinical benefit to patients.

Here is where we identify the reduction in risk of all-cause mortality or first hospitalization, is how it is presented, and then we go onto define how hospitalization was used in that trial, including

noting that the hospitalizations did not include the device implant attempt or any reattempts. We also identified the reduction and risk of all-cause mortality and we mentioned the reduction of heart failure symptoms.

The Panel also made a number of other recommendations with respect to the labeling and, in particular, they were interested to see how we were going to be presenting hospitalizations. While they agreed that the representation of the primary endpoint should not include the index or implant hospitalization, they felt that it would be important to present in clinically meaningful information to physicians and patients that describe hospitalizations in general.

And so this is an example of the approved labeling that we've worked with the company to develop. This is the original Kaplan-Meier curve for the primary endpoint of all-cause mortality or first heart failure hospitalization and this is the same as what you would see in the published literature. But the labeling also represents a number of

hospitalizations per patient year and that was done to account for the difference in follow-up for the two different groups.

It presents this information comparing the OPT or the control group to the CRT-D group and it also gives you an idea of the relative contribution of the implant hospitalization in both cases. There is also a graph in the labeling that depicts the number of hospitalization days per patient year, again distinguishing between the OPT group and the CRT-D group and also indicating a relative contribution of the implant hospitalizations that occurred in both groups.

And finally, there is a representation of the number of heart failure hospitalization days per patient year comparing the OPT group to the CRT-D group. Based on their Panel recommendations, the FDA approved the companion submission on September 14, 2004.

Now, moving on to the Philips Medical Over-the-Counter AED, the FDA raised a number of concerns to the Panel that day including asking

whether the data was sufficient to support over-the-counter availability of the device and, in particular, we wanted them to comment on the adequacy of the user testing and whether the sponsor had appropriately integrated CPR prompts and notifications to dial 911 or to notify the Emergency Medical Services.

We asked the Panel to comment on whether the data were sufficient to support over-the-counter availability of the pediatric pads. We asked broadly for labeling recommendations and to comment on the sponsor's methods for tracking devices in the event of a recall or adverse event reporting and whether they believe that a post-market study would be required. Because this was a 510(k) application, there was no vote. However, the Panel was felt to be generally in favor of over-the-counter availability of the device. They felt that the usability testing was adequate and that the voice prompts for CPR and the visual prompts for calling 911 were felt to be adequate.

There was no consensus, however, on whether the pediatric pads should be available over-the-counter. There were quite a number of specific

labeling recommendations that were given to us and the Panel recommended a post-market study, but asked FDA to review the tracking and adverse event reporting methods. FDA ultimately concurred with the Panel that there was sufficient usability testing and we did not require additional testing on the part of the sponsor. We felt that the prompts for CPR were appropriate and with minor modifications to the 911 reminders we felt that they were appropriate as well.

Importantly, the pediatric pads were not included in our over-the-counter decision and they still remain available as a prescription accessory. And that was done for a number of reasons. We felt that ultimately this would simplify a very complex purchasing decision by not offering too many options or accessory products to the user. We felt that it sent an important message that underscores that sudden cardiac arrest is an adult public health concern, one that's not shared equally by the pediatric population.

We feel that this decision ensures safe and effective use on both adults and children. And we felt that this was not going to impact availability

too detrimentally of families who have higher risk children, because those families should be well-integrated into the medical system and would easily be able to get a prescription for the products.

We made substantial labeling modifications based on Panel recommendations. I'm not going to go through all of them, but I'll give you one example. The Panel felt that the outer box should be designed to help customers make an informed purchase decision and these are some of the things that appear now on the outside of the box and also appear on websites that are offering this product for over-the-counter sale.

For example, it mentions that you should speak to your doctor and that a defibrillator does not take the place of seeking medical help, that you can't use the device on yourself, that users may need to perform CPR, that responding to cardiac arrest may require you to kneel, that voice instructions and materials are in English and that the HeartStart provides audible and visible indicators for maintenance.

FDA's clearance decision included acceptance of the sponsor's methods for post-market tracking and adverse event reporting and we're continuing to work with the sponsor on developing the Post-Market Study Plan. Ultimately, FDA cleared this product for over-the-counter use on September 16, 2004. Thank you very much.

ACTING CHAIR MAISEL: Thank you, Megan, for those updates. At this point, we will begin the open public session of this morning's meeting, both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making to ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct

competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. At this point, I would like to invite Dr. Rodney White to approach and address the Panel.

DR. WHITE: Thank you very much. It's a pleasure to be here today. I'm representing the Society for Vascular Surgery and a project that you have heard about before, I think, that we would like to update you on. The Lifeline Registry, which now is the SVS/American Vascular Association Outcomes Registry has been an effort that we have updated Panels on serially related endoluminal grafts.

At the beginning of this, I would like to tell you that my Conflicts of Interest are that I have

no commercial interest in Gore. I'm not a Gore investigator. I am here representing the Society for Vascular Surgery as the Secretary and Chairman of the SVS/AVA Lifeline Registry Committee. I'm an academic surgeon. I make my living treating these kinds of patients and get promoted based on publishing papers, so I think my major conflict is I make a living doing this sort of stuff.

The Lifeline Registry was established in 1997 to look prospectively at post-approval of abdominal aortic aneurysms. The SVS has now recently, in association with the American Vascular Association, an expansion of our nonprofit foundation efforts, extended the SVS capability to look at outcomes analysis, not only to the endoluminal grafts, but to the technologies we're talking about today, thoracic grafts or in a concurrent effort to carotid stents and endarterectomy.

A unique aspect we offer is that we can look at both of these technologies concurrently and in that regard, we would like to emphasize from the beginning that the SVS is going to make a specific

effort to make available operative data related to these technologies, so as we move into these other areas, it will be relevant.

Registry is unique in that the initial attempt was to do something that hadn't been done successfully previously and that was to look prospectively to establish a registry that would take scientific data, put it together over time and actually look at a number of stakeholders involved in this, including the societies and clinicians, the foundation that I mentioned, federal agencies, and we have been very fortunate to have both FDA and CMS active in these efforts with their input.

An industrial advisory committee made of, in this case, the following companies which have supported that effort, I will emphasize that of the group today W.L. Gore was a founding member of the registry, has been very proactive in supporting this effort and that this has been an important part in how we progress. The registry goals were to evaluate long-term and prospectively endoluminal graft function.

Because of the requirement for post-market surveillance, I think this is a topic that will come up later, we were able to establish with a central registry committee working beneath the foundation and again with the ex officio input of the FDA, NIH, CMS and this industrial advisory committee and our data center, New England Research Institute, a way to be able to collect this data, put it together and report it.

The funding mechanisms are by the foundation itself and industrial partners feeding this data and collecting it. The registry then initially was to look at the post-market IDE data, collect that and look at it over the five-year surveillance interval that was available. Now, if you think about that, that makes it a very high compliance audited data set. There are then two parts to this registry I'll tell you about briefly, because we've got now six-year results to look at, was to take this five-year PMA model, look at these patients over time and because of the post-approval market, we're able to look at the requirement of the Agency to have the

manufacturers submit this data and work out a collaborative effort to collect this.

The long-term results of the FDA devices have then been evaluated and in a collective fashion you will see. Now, these are just some numbers to give you an idea of how these can be powered over time, but with four approved devices and some commercial site entries, you will see we're now nearly at 3,000 patients. A very important part of this is we also have a concurrent surgical control group of patients that can be compared for outcomes analysis. And in the kinds of considerations we're doing today, these are particularly important.

Primary and secondary endpoints that I won't list in detail were looked at and were able to, in almost all cases now, start to look at very important outcome issues and patient selection parameters and have reached statistical significance in many of these related to the outcome comparing endoluminal grafts to the conventional stent graft technologies. The same for hospital parameters, ICU stays, things that are routinely looked at and again

we can compare these two groups.

What we have come up with then, now, these are six-year curves, are comparisons of morbidity, mortality, aneurysm-related mortality, freedom from rupture, gender analysis, this has been highlighted in other examples, freedom from surgical conversion. And again, just to highlight this very briefly, there is a data set that was presented at the SVS this year in a publication submitted to the Journal of Vascular Surgery that will summarize these six-year data outcomes and forward. But in general, it gives us a very good standard to be able to apply this to and have a surgical cohort group.

Now, the other important relevance to today is not only if we looked at the PMA data sets, but we've tried to extend this to clinical sites outside of the use and studies. There are currently 15 centers entering that data and we've also, in collaboration with the Canadian Vascular, have 22 Canadian sites that are submitting data to the registry. So this becomes very powerful. At some extent, we tried to simplify that and make it

automated where the sites would, in an automated fashion, enter their data, the reports go then, and this sort of prototype fashion, to look at critical measurements related to an endoluminal graft.

I know these are hard to see, but it would be diameter, volume, distance from an anatomic landmark, anything that deviates over time, and these are sequential intervals highlighted in red. There's a possibility to put in images, so you can look at sequentially patient records. In a thoracic prototype relevant to today, we could do a similar sort of entry looking at fixed points, measurements, volumes and diameter, put in sequential records, collect these that can be given to the patients, put in their charts and used for data or in the carotid scenario that I mentioned as an outcomes, do a similar sort of thing where we can look at critical parameters in operative carotid stent patients, collect the data, have imaging analysis, in this case, the patient has had an event after that and be able to correlate all this data.

So that the summary would be then that the SVS has had now a six-year track record in

collaboration with the Agency and industry to do this. We would like to present it as a future prototype and that the SVS is committed to making outcomes analysis related to temporary and new devices a priority for our society. Thanks for the opportunity to present this material.

ACTING CHAIR MAISEL: Thank you for your comments. The next invited speaker or public speaker is Dr. Greg Sicard.

DR. SICARD: Good morning. I'll be very brief, since Dr. White already presented a lot of the data that is supported by the Society for Vascular Surgery. But my name is Gregorio Sicard. I'm a practicing vascular surgeon from Washington University School of Medicine in Saint Louis and currently the President of the Society for Vascular Surgery. I do not have any financial interest in W.L. Gore or the specific product and my trip was paid by the Society for Vascular Surgery.

I come here today primarily representing the Society for Vascular Surgery and secondarily as a practicing vascular surgeon. The Society for Vascular

Surgery has over 2,300 members, many of which care for patients that have thoracic aortic aneurysms and fully understand the impact that a less invasive approach for the treatment of this condition will have.

As a vascular surgeon who for many years has practiced both open and endoluminal treatment of the intrarenal abdominal aortic aneurysm and open repair of aortic abdominal aneurysms, I rise to comment on the benefits of making this technology available for patients with this disease. The introduction of endoluminal prosthesis for the treatment of intrarenal abdominal aortic aneurysm has had a significant impact in patient care because of the decrease perioperative mortality and morbidity associated with this less invasive technique.

This has been recently documented in AAA randomized trials from both the United Kingdom and Holland. The approval of a thoracic endograft device will add an important option for cardiothoracic and vascular surgeons who treat patients with these conditions. Even in experienced hands, the surgical treatment of thoracic aortic aneurysms carry a 5 to 10

percent perioperative mortality and a significant morbidity estimated between 50 and 75 percent that is, obviously, associated with prolonged hospitalization and increased health care cost.

This less invasive technology offers a new approach that is associated with lower operative and post-operative mortality and morbidity. Therefore, I strongly urge this Panel to approve the thoracic endograft device. This lower risk treatment modality will provide significant benefits to patients as well as expand the options that treating physicians can offer to this patient population. Thank you for your attention.

ACTING CHAIR MAISEL: Thank you. Is there anyone else in the audience who wishes to address today's Panel? Please, approach. Please, identify yourself and mention any financial conflicts.

MR. TINKER: My name is Bill Tinker. I'm a patient of Dr. Bavaria. I've had no contact until today, I've met some of the people from Gore and I want to let you know that I'm here because I wanted to be here. I survived. I had an attack where I went to

surgery to repair an aneurysm, an abdominal aneurysm. Back in June of last year, I had a large aneurysm in my chest, told to be inoperable and I was given two weeks to live. So I opted for the stent and it worked and now I'm here.

With four or five years in between, I suffered with the aneurysm. You have to understand it's not easy. I couldn't pick up anything larger than 20 pounds. I drove in the right hand lane off the road, because I knew once it blew I would have 10 seconds to get off the road before I killed somebody. Now, I'm driving in the passing lane. That in itself is really nice. It's good to have this happen and I want you to know that it's traumatic what I went through in the open-heart.

Yes, and the open surgery was -- it was a month in the hospital. My kidney shut down three times. My valves shut down. My lungs shut down. They contacted my family on two or three occasions that I was dying and I just kept coming through and coming through and a month later they woke me up and it was a year later before I could walk 100 feet to my

mailbox to pick up my newspaper and my mail. It was that long in recuperating.

Two days after I had this sort of massive aneurysm, after I received the stent, two days later I was ready to go home. And I was absolutely pain-free. There was no pain. And to this day I'm able to loft around 50 pound bags of cracked corn and salt and no problem at all. It's just amazing and it's still ticking and it actually looks like a barbed-wire fence, but it works. And I just wanted to let you know.

I had one other thing I wanted to make a point or two. I hadn't mentioned those people. Back in '99, I had a 2 inch patch put in my abdomen and I went through all that trauma and close to death several times, that bill came to $500,000 for a week stay in intensive care. Back this June when I had this done, well, the amount was $90,000, but it wouldn't have been that high if they had had that ready for me when I went in. I had to go through a lot and stay in the hospital, that ran it up.

But I'm estimating it would have been

$50,000 tops. So we're talking 10-fold savings we're going to have with this. Patients are going to be able to have this without their insurance company going broke. And I want everybody to have it as well as I did and have a good as a life as I do. Thank you very much for listening to me.

ACTING CHAIR MAISEL: Thank you very much for your comments. Is there anyone else in the audience this morning who would like to approach? Yes?

DR. CAMBRIA: Good morning. My name is Richard Cambria. I am a Professor of Surgery at the Harvard Medical School and Chief of the Division of Vascular and Endovascular Surgery at the Massachusetts General Hospital in Boston.

I traveled here today at my own expense. I have no financial interest in the W.L. Gore Company or its products, although our group and our institution has received support in the form of the support for conducting clinical trials from the W.L. Gore Company and virtually every other device development pivotal trial in abdominal aortic

aneurysms and thoracic aortic aneurysms. We currently participate in all three extant thoracic aortic aneurysm stent graft trials.

Our group at the Mass General has embraced stent graft repair of abdominal aortic aneurysm and thoracic aortic aneurysms. We currently treat, approximately, 350 aneurysms of all types annually at our hospital. We implanted the first stent graft for an abdominal aneurysm in New England in 1994 and the first thoracic stent graft in 1997.

To date, we have implanted some 900 abdominal aortic aneurysm stent grafts and over 100 thoracic aneurysm stent grafts. We have participated in virtually every pivotal trial to evaluate stent grafts including, as mentioned, all of those for the thoracic aorta.

My own practice has centered on thoracic and complex thoracoabdominal aortic aneurysms and, in that context, I have personally performed over 500 open aneurysm repairs of the thoracic and thoracoabdominal aorta. Thus, we speak from a position of, I think, some experience and I guess we

would like to think expertise in this field.

Our practice has evolved to the point where some 65 percent of abdominal aneurysms are treated with stent grafts, and I personally treat every thoracic aneurysm where such treatment can be performed with a stent graft, as opposed to an open operation. We are, of course, currently limited in the application of stent grafts in the thoracic aorta to those patients who qualify for the available FDA-sponsored clinical trials since, of course, there is no commercially approved device.

I would just remind the Panel that today we focus on degenerative aneurysm of the thoracic aorta, but this is just the beginning. There is a whole host of thoracic aortic pathology, including traumatic lesions, traumatic tears and aortic dissections, and I am certain that we will see stent graft repair play a very important part in the treatment of all of these pathologies over the next few years.

In virtually every comparison of endovascular therapy, as opposed to conventional open

surgery, issues of safety, efficacy and durability are, of course, prescient. None of these endpoints can be separated from what I refer to as the morbidity quotient of the procedure, namely, what is the risk of the treatment?

In certain vascular lesions that these Panels have heard, for example, the issue of carotid artery disease, there is, in fact, a very narrow margin, if any, between the morbidity quotient of open surgery as opposed to endovascular therapy. The opposite end of the spectrum is true for the treatment of thoracic aortic aneurysms.

Open surgical repair of thoracic aortic pathology, although refined at the moment to a high level of sophistication, is still accompanied, even in the hands of experts, by major morbidity in the form of death or paraplegia in some 10 percent of patients. Thus, the morbidity quotient of the pathology that we are talking about here today is extreme in the difference between endoluminal therapies and open surgical repair.

ACTING CHAIR MAISEL: Dr. Cambria, if you

could conclude your remarks in the next minute, please.

DR. CAMBRIA: Yes, I will.

ACTING CHAIR MAISEL: Thank you.

DR. CAMBRIA: Yes, I will. Patients need this pathology, this technology. We who treat these patients absolutely require it. This will be the single significant advance in the treatment of thoracic aortic pathology in our lifetime. Thank you for your attention.

ACTING CHAIR MAISEL: Thank you very much. Are there other individuals who wish to approach? Yes?

DR. TUCHEK: Good morning. First of all, I want to let you know that I have no financial interest with Gore. I'm here on my own time and at my own expense. My name is Dr. Michael Tuchek. I am a cardiovascular and thoracic surgeon at Loyola University in Chicago, Illinois.

Loyola has got one of the largest open heart programs and largest aortic surgery programs in the city. I guess I'm one of the few people in the

audience like Dr. Cambria, one of the old fashioned surgeons who still do a lot of open procedures.

I am also fortunate enough to be one of the busiest endovascular surgeons in the country. I did more Medtronic AneuRx devices than any surgeon in the country last year. I am one of the primary investigators in the Valor Trial for thoracic stent grafts and I am a leading enroller in that trial currently. So I am being blessed with being able to do both the open procedures and have a lot of experience with stent grafting also.

Obviously, because I am in the Medtronic Trial, I am not involved with Gore. I am not in their trial. I have never placed their device. I have seen it placed once and that is my total experience with Gore. I am sure in the audience there's a few Gore people who are a little concerned about a Medtronic guy being here talking about their device but, rest assured, I'm not here to torpedo their efforts. I am here to applaud them.

We have all looked at the Gore data and you are going to be looking at it in detail shortly.

I'm not going to go over it, but I reviewed it. I think they did a great job in this trial. I think that when they had issues, they dealt with them. They never jeopardized their patients' care while the trial was ongoing and I applaud them for that. I hope that the Medtronic trial is doing just as well as this trial was.

When I started doing abdominal stent grafts in 1999, I thought the trial that was going on, and when it got approved, I thought the technology was slick, the word I used. When you look at open operations, they are fairly morbid. When I started doing thoracic stent grafts, I thought that technology was nothing short of astounding, truly astounding. My son calls it radical, but I use the word astounding. It is truly impressive technology.

When I do an open operation, for those of you who are not cardiac surgeons, we make incisions from the back of the neck all the way down to the naval. We break ribs or resect ribs. They go on a heart-lung machine frequently. We resect the aneurysm. There is bleeding. There is a lot of

morbidity associated with the operation.

And in a week or two, if the patient does well, a lot of them go home in wheelchairs, paralyzed permanently, and that is when the operation goes perfectly. That is an issue. There is a lot of morbidity associated with the open operation and it's a fine operation. I love that operation, but there are still significant issues with it.

When I take a patient for a thoracic stent graft, I make a one inch incision and in a day or two, that patient walks home. I have had no paraplegic patients. I have had no strokes. Knock on wood, I hope I don't have any in the future. It's truly an astounding technology.

This is critically needed technology and is far and away, I believe, better than the open operation and it hurts me to say that, because I'm a surgeon who loves to do open surgery. We need an endovascular alternative to treat these sick patients, and I implore you to recommend that this device get approved.

If and when it does get approved, and I

hope that's soon, I think it needs to be restricted to the busiest centers, those centers that do a lot of open surgery and that have a lot of experience in endovascular stent grafting. I don't want to see any learning curve disasters, I think, that may be unlike or maybe like the carotid post-market surveillance work that is going on.

We need to have something like that here for 18, 24 months, have the most experienced people doing this procedure, giving good long-term follow-up results. And I think, ultimately, we'll find that this technology far and away exceeds what we can do in doing an open operation. As a busy open and endovascular surgeon, I want this technology, but my patients desperately need this technology. Thank you for your attention.

ACTING CHAIR MAISEL: Thank you. Are there any other individuals that would like to address the Panel?

DR. KARMY-JONES: Good morning. Thank you. My name is Riyad Karmy-Jones. I am a cardiothoracic trauma and now an interventional

radiologist and cardiothoracic trauma surgeon at Harborview Medical Center at the University of Washington, Seattle, and unfortunately I have no financial attachment with Gore.

I just wanted to speak from two relatively known perspectives. Harborview is the only Level I trauma center for the WAMI region. We are effectively the county hospital for Washington, Alaska, Montana, Idaho and so on. The bulk of what we see in thoracic vascular and particular others are emergencies usually coming in at night.

So the two things I would like to talk about are much of which has been alluded to, is these devices can be placed very quickly, even quicker than an open operation, which can be critical in a patient with a complex leaking thoracoabdominal or thoracic aortic aneurysm. It does reduce the stress in these patients many of whom are actively being resuscitated as they present over minutes or hours to our institution, and we believe that there is a marked benefit for an endovascular approach.

And then I would just like to flip to the

other side just very briefly, is that to consider that most of these devices are compared to open repair, but there are significant complications associated with medical therapy for these lesions, end organ failure, rupture, renal failure. We see patients who are presenting with bowel ischemia and renal failure and stroke because of prolonged aggressive medical management and are not candidates for the open repair.

So I think that these devices ought to also be considered as offering potentially a significant advantage over medical management in many cases for some of these patients. Thank you very much.

ACTING CHAIR MAISEL: Thank you. Is there anyone else who would like to address the Panel? At this point, we will close the open public hearing.

DR. ZUCKERMAN: Dr. Maisel, can I ask one question to the Panel?

ACTING CHAIR MAISEL: Of course.

DR. ZUCKERMAN: We began this open session with a very nice presentation from Dr. Ashar of FDA talking about a general construct for the Critical

Path Initiative and some ideas that the Agency has for streamlining the translational process. We then got more specific with the work that Dr. White and the SVS have done recently in the AAA area.

While it's not the intent of the Agency to specifically endorse a particular registry or approach, my question though to the Panel members is when data like these are accumulated, and this Panel has looked at multiple AAA sponsor submissions, could these data be utilized instead as a control data set? Is it worthwhile to really actively examine other options in the AAA area? Any general responses would be appreciated.

ACTING CHAIR MAISEL: Dr. Somberg?

DR. SOMBERG: It's always useful to have comparative data and I think it can be very helpful, but in the early stages it's also very important to have control trials and a randomized base, and I think while we move into this, it's the case in drugs, it's the case in devices, as we move into a field it's always more arduous for the first carriers of the spear than the people who come behind, the mopping up

after operations and all, no pun intended.

So I think while it can be useful, there is the other side of the coin, which is that there is a responsibility for those who are initially introducing a device, a technique or another therapeutic entity to try to have that in the context at least of one control trial, preferably a randomized one.

ACTING CHAIR MAISEL: Mitch?

DR. KRUCOFF: Yes. Bram, I think the spirit of the question has its own answer. Of course, they can be useful. We just have to be smart about how useful and when and where. And the two things that I think will be important drivers of that, one is just the opportunity to take proprietarily owned data sets and compile them is itself an organization issue we have struggled with on other fronts like stent data.

The other is just to stay, as I know you would very clearly, aware of how long a time period these different data sets are aggregated over, so that data from the '80s or the '90s, how much of a time

change there is in collecting some of these less numerous cases.

ACTING CHAIR MAISEL: Dr. Johnston?

DR. JOHNSTON: I would echo some of those concerns, but as a member of the Society for Vascular Surgery and having looked at the data set, it is now maturing nicely and it is much more sophisticated in terms of data collection and openness than it was a couple of years ago, for example, and so I think that you will find this data set extremely useful in the future.

ACTING CHAIR MAISEL: Dr. Nicholas?

DR. NICHOLAS: I think there is a real use for this information, and I would recommend that we consider not only the time interval of this control surgical group, but also use it only up until the point where we see that there are some major new changes in open surgical techniques. This operation for open intrarenal aortic aneurysm is pretty well standardized and until something new comes along, I think it would serve to be a control group.

What I would recommend is that the initial

effort to do this would be to combine a look using the Lifeline data as well as a contemporary control group for the first study or two to see if the hypothesis holds.

ACTING CHAIR MAISEL: Dr. Normand?

DR. NORMAND: I would just agree with Mitch very strongly, with his answer, but I would echo that not only is it the quality of the data that's collected. I think it would be very clever about the analytical methods that you're using. There is a lot of selection issues that I think a straightforward simplistic analysis is not going to be worthwhile.

So I think it's a great idea to use more data, but I think many people are going to have to be more open-minded about the analytic strategies you will use because of the huge selection issues in a registry database.

ACTING CHAIR MAISEL: Very well. So at this point, we will close the open public hearing and I would like to invite the sponsor to begin their presentation.

MR. NILSON: Thank you for being here

today. My name is Mike Nilson. I am the product specialist for the GORE TAG Thoracic Endoprosthesis. We will refer to this as the TAG device throughout the remainder of the day. Also presenting with me today are Dr. Scott Mitchell and Dr. Michel Makaroun. Both Dr. Mitchell and Makaroun were principal investigators in our clinical trial program.

Dr. Mitchell will present both etiology and current therapy. I will present device history and design. Dr. Makaroun will present the clinical data, and then Dr. Mitchell will present the risk/benefit profile for the TAG device.

We are here today to request a recommendation for approval of the TAG device for the indication of endovascular repair for aneurysms of the descending thoracic aorta. Currently, there is no FDA-approved thoracic endovascular device to meet this therapeutic void. In the next presentation, Dr. Mitchell, who is a professor of cardiothoracic surgery at Stanford University, will discuss the etiology and current therapy of aneurysms in the descending thoracic aorta.

DR. MITCHELL: Thank you, Mr. Nilson, and good morning. First, I would like to clarify that as one of the co-principal investigators, that I have served as a consultant to the Gore Company for the last several years. However, other than that, I have no financial relationships with Gore nor any proprietary patent royalties.

This morning we will be discussing aneurysms, specifically aneurysms of the thoracic aorta. An aneurysm may be defined as a local or a focal dilation and weakening of the aortic wall, which is secondary to many processes. Today we will discuss primarily degenerative aneurysms, those that occur as a result of the ravages of hypertension and arteriosclerosis.

An aneurysm or rupture of the aorta, both the thoracic and the abdominal aorta, is estimated to cause 32,000 deaths annually in the U.S. To put this in perspective, breast cancer accounts for 41,000 deaths annually.

After Juan Perotti first described an endovascular approach for abdominal aneurysms in the

1980s, Gore became involved with the development of endovascular repair for aneurysmal disease in 1994 and in 1997 initiated the clinical evaluation of abdominal and thoracic endoprostheses.

By 2002, the Gore EXCLUDER device was approved for the repair of abdominal aortic aneurysms and by 2004, there had been over 20,000 EXCLUDER implants worldwide. In 2005, we now have the opportunity to have the TAG device considered for FDA approval.

The area that we will address today is the descending thoracic aorta, an area uniquely suitable for endograft technology because of its relatively straight course with few side branches. It is bounded by the transverse arch superiorly and the diaphragm interiorly. Neighboring vessels of the distal arch include the left subclavian artery and just below the diaphragm, the celiac axis.

Thoracic aneurysms may be either focal or diffuse, but they share one critical natural history phenomena and that is that of continued dilation until they eventually rupture, and the goal of all our

therapies, open or endovascular, is to prevent aneurysm rupture and death. Although most aneurysms are asymptomatic, some present with symptoms with pain, compression of the esophagus or traction on an adjacent nerve.

There are, approximately, 15,000 new cases of thoracic aortic aneurysms diagnosed yearly, which results in over 5,000 surgical repairs. Nevertheless, there are still an estimated 2,500 deaths annually from rupture in the U.S. We have good outcomes data from probably the most studied county in the U.S., that of Olmstead County in central Minnesota.

Over the 1960s and '70s, there was a fairly uniform incidence of thoracic aortic aneurysms of about three per 100,000, but in the two recent decades, we have seen an increase to now about 10 per 100,000. Whether this represents a true increase in incidence or it reflects our aging population or perhaps even our increased diagnostic capabilities is unknown.

However, we do know several things and that is that the risk of rupture is increased as the

aneurysm grows in size. It's increased in older patients and in patients who have concomitant emphysema or COPD. Additionally, patients who present with pain over the rapid increase in size are at increased risk for rupture.

And so that we can see on the bottom line of this graph, if your aneurysm is less than 4 centimeters, your risk of rupture at five years is fairly nominal, 3 to 4 percent. But if your aneurysm exceeds 6 centimeters in size, there is about a 10 percent incidence per year rupture with over 30 percent having ruptured at the end of a three-year interval.

These slides depict a fairly typical mid descending thoracic aortic aneurysm with a magnetic resonance angiogram on the left, the surgical exposure of the same aneurysm through, as you can imagine, a fairly broad incision to get this type of anatomic exposure. You need room to operate on these patients safely and by these approaches, you inflict significant morbidity as has been referenced in some previous remarks. With adequate exposure and good

technique, you can affect a very effective surgical repair as seen on the right.

One problem with surgical repairs is that they are morbid and the older the patient, the worse the morbidity. Increasing age and the frequently concomitant pulmonary disease puts these patients at highest risk, which presents surgeons with the dilemma that it is the older, sicker patient who most needs the operation, but it's that same patient who is most at risk for catastrophic complications.

The open surgical repair is effective and durable, but it does exact a significant toll. Mortality in this series was 6 percent. 14 percent of patients experienced paraplegia, and there was a 70 percent incidence of cumulative morbidity, that is the number of patients who incurred any major complication in the postoperative period and recovery is frequently protracted.

Patients, as we have heard, are fearful of this operation. They frequently have lived independently and now to suddenly be debilitated is a major problem for them and many refuse operation. We

saw a fairly significant onslaught of these patients in the early 1990s at Stanford University and were impressed with the age and comorbidities.

We teamed up with our interventional colleagues and formed our own thoracic stent graft program, which was approved by our own IRB for high risk patients. We constructed a hybrid device from FDA-approved Z stents covered with an improved Dacron graft and began a high risk trial, which resulted in 103 patients being treated.

By our own estimates, 60 percent of these patients were absolute nonoperative candidates with either unstable coronary disease, very severe obstructive pulmonary disease or two or greater previous attempts at repair. Indeed, we expected a surgical mortality with open procedures exceeding 30 percent, and our 9 percent endovascular mortality we thought was quite respectable and prompted us to continue more investigations.

The fundamentals of endovascular repair are fairly straightforward. It's a minimally invasive procedure usually through an incision in the groin or

a small flank incision. We now can reliably deliver and deploy endovascular devices whose hemostatic seal excludes the aneurysm from the circulation and, thus, prevents aneurysm rupture.

This is an angiogram of our very first TAG device patient, a very pleasant 72 year-old woman who had presented with a rather dramatic increase in size. And as you can see from the angiogram on the left, this is a pretty sizeable aneurysm, which is completely excluded by the fourth postoperative day when she left the hospital.

In summary, 6 centimeter aneurysms of a thoracic aorta have a rupture rate of, approximately, 10 percent per year. Open surgical repair is effective and durable, but the cumulative morbidity of 70 percent or greater and our own 6 percent mortality remains substantial and there are other limitations. The early results of thoracic endovascular repair showed potential patient benefit. I would like to return the podium to Mr. Nilson.

MR. NILSON: The TAG device has been thoroughly studied. We began implanting the device in

the U.S. in 1998 beginning with a feasibility study, TAG 97-01, followed in 1999 by the pivotal study, TAG 99-01. Due to fractures in the deployment wire, Gore chose not to pursue FDA approval until we could modify the design to minimize the likelihood of these wire fractures. Consequently, in November of 2001, Gore voluntarily withdrew the device from commercial distribution and the device was modified. I will describe those modifications in a minute.

After the modifications were completed, Gore conducted a confirmatory study, TAG 03-03, designed to confirm the preclinical test results of the modified device. A treatment IDE, TAG 04-02, allows study centers access to the device pending approval and is currently ongoing. We have five-year follow-up data on patients in the feasibility study and two-year follow-up on those in the pivotal study. The confirmatory study finished follow-up in August of 2004, and we're continuing to follow all patients through five years.

Between 1998 and 2001, 2,800 original devices were implanted in over 2,100 patients, mostly

in Europe. During the period of device modification from November of 2001 until November of 2003, the use of the original TAG device was limited to nonsurgical patients in three centers in the U.S. Since November of 2003, over 1,500 modified devices have been implanted in over 1,100 patients, again, mostly in Europe where the device has been commercially available since March of 2004.

Notice from the numbers that most patients received more than one device. Today we will focus on the U.S. clinical trial data. The picture you see is the original TAG device, which was designed with the deployment wire, also referred to as a spine, and is highlighted by the red box. The purpose of this wire was to provide longitudinal support during deployment. It counteracted forces due to blood flow during deployment until the device engaged in the aortic necks. Once the device was seated into the necks, the wire had no further design function.

As mentioned previously, this wire had a higher than anticipated fracture rate. The deployment wire fracture rate was 32 percent in our longest term

test cohort patients. Only five out of the 44 patients who have been identified with fractures have clinical sequelae associated with these fractures. These reported sequelae are endoleaks, predominantly Type III. We used information gained from the clinical use of the original design to design tests to replicate the failure mode and ultimately leading to the modification of the TAG device.

At this time, I would like to hand out samples of both the modified and original TAG device and I will collect these samples after my portion of the presentation. For everybody in the audience, I'm going to allow the Panel two minutes to look at these devices before I start my presentation up again.

MR. MORTON: Mike, can we take them out of the bags?

MR. NILSON: Yes, you can remove the devices from the bag. They are in the bags, because there is a paired sample of an original and modified device in each bag.

ACTING CHAIR MAISEL: I think you can continue with your presentation while the Panel is

looking at the devices.

MR. NILSON: Okay. Gore minimized design modifications in order to maintain device attributes and clinical performance while eliminating the deployment wire. The modifications did not change the device's fundamental design. To compensate for the loss of this deployment wire, the graft material was strengthened.

The original TAG device graft material was constructed from two fluoropolymer layers. The modified TAG device is constructed from three fluoropolymer layers. The additional layer, which is similar to that incorporated into the marketed EXCLUDER Bifurcated Endoprosthesis, is sandwiched between two original layers and this layer provides the longitudinal stiffness that was formerly provided by the deployment wire.

The TAG device is a symmetrical tube consisting of a nitinol self-expanding stent and a fluoropolymer liner. The stent is attached to the liner without sutures by trapping the wire between the liner and the attachment film. Flares are located on

both ends of the device to aid in conforming to tortuous anatomy. Sealing cuffs on both ends of the device help exclude the aneurysm from circulation by eliminating endoleaks. At the base of the flares are two radiopaque gold bands, which aid in placement and follow-up.

There is a deployment sleeve, which constrains the device on the end of the delivery catheter and remains permanently attached to the device after deployment. The TAG device has a flexible 100 centimeter working length catheter to access the descending thoracic aorta from the groin. Radiopaque olives at both ends of the device protect the device during insertion and manipulation, as well as facilitate position.

A fluoropolymer deployment sleeve constrains the device on the leading end of the delivery catheter. There is a guidewire port that accommodates .035 inch guidewires and a flushing port that removes trapped air from the guidewire lumen.

A deployment knob is located at the control end of the catheter and has a deployment line

that runs the entire length of the catheter connecting the deployment knob to the deployment sleeve. Pulling this knob releases the device from the catheter at its desired target. The delivery catheter and deployment method remains exactly the same as the original device.

The following animation shows how the TAG device is delivered to its desired location within the body. You will see an aneurysm in the descending thoracic aorta distal to the left subclavian. That is an .035 inch guidewire accessing across the aneurysm. The device is being advanced and positioned to its desired target and the deployment is initiated in the middle and extends to both ends, again in slow motion, and this facilitates a very accurate deployment.

The following video shows a real time deployment of a TAG device in a patient with an aneurysm in the descending thoracic aorta. Because the deployment is rapid, this video will repeat the deployment sequence several times in succession. On the top course of the screen, you will see the deployment of a TAG device. If you're having trouble

seeing it, notice the curved shape the device has constrained on the end of the delivery catheter.

Once the device is released off the catheter, it conforms to the anatomy. Risk analysis was performed to determine potential effects of this device modification. This analysis was essential in determining testing requirements to verify that device modifications would not adversely effect device performance. The TAG device has been extensively tested in our Comprehensive Testing Program. This testing included newly developed durability tests that replicate the deployment wire fractures.

The requirements deemed appropriate were developed through a combination of established ISO standards and collaborative efforts between industry and the FDA. These tests assure the TAG device functions as intended, which is to exclude aneurysms from circulation and prevent aneurysmal rupture. This is an example of one of our many durability tests. This test was specifically developed to replicate the deployment wire fracture. Notice the extreme curvature of the spine in the original device in the

lower left. To confirm these results related to the device functional performance, poor conducted or limited clinical trial, TAG 03-03, we'll even call the confirmatory study. We will now collect the samples.

In the next part of our presentation, Dr. Makaroun, who is a Professor and Chief of Vascular Surgery at the University of Pittsburgh, will present results from our Clinical Trial Program.

DR. MAKAROUN: Thank you, Mr. Nilson. Good morning. I would like to start by declaring that I do serve as consultant for W.L. Gore and I have received both educational and research grants from W.L. Gore as well as just about any other manufacturer in this field.

It really gives me great pleasure to be here today on behalf of all the investigators that participated in these clinical trials to share with you the results of the three phases of the TAG development that so far have spanned over seven years, over the first device being implanted in February of 1998. All the investigators, as well as myself, have looked forward to this day with much anticipation and

the hope that we can finally bring this technology to our patients.

The first study was the feasibility study that started in 1998 and concluded enrollment in 1999. This study was carried out at two sites in the United States and in all enrolled 28 patients with descending thoracic aneurysms. The mortality at 30 days was only one patient or 3.6 percent. For one year, the mortality was 21 percent with no incidents of paraplegia or stroke. Renal failure and myocardial infarction was noted in only one patient each or 3.6 percent.

Through a five-year follow-up period two additional AEs long-term were reported between two and five years. All-cause mortality at five years was 25 percent. Endoleaks were noted at any time in 21 percent of the patients and was a growth in 18 percent, fractures in 32 percent. There was one conversion and two reinterventions over time to replace additional devices.

None of the following events occurred during the follow-up. There were no aneurysm

ruptures, migration, extrusion, erosion, lumen obstruction or branch vessel occlusion over time. These encouraging results left the development of the pivotal Phase II Trial, the 99-01 Trial, that started enrolling patients in 1999 and completed enrollment in May of 2001. The pivotal study was a multicenter study that was carried out at 17 clinical sites in the United States and was designed to be non-randomized with a control arm.

The test subjects were all treated with a TAG device and were compared to post-subjects that were treated by the traditional open surgical repair. One-year clinical endpoints were used for the analysis, but all patients were to be followed for five years and the follow-up is still ongoing. The control group were all enrolled from the same sites as the patients undergoing the TAG device. They were in two groups, 44 patients were enrolled concurrently with the device during the study, in addition to 50 patients that had recently undergone open repair at the participating centers.

This strategy actually was quite

successful in generating probably one of the largest series of isolated descending thoracic aneurysms available for comparison. To limit bias, the historical cohort was enrolled by working facts sequentially from the last patient that was treated prior to the initiation of the study. And a goal was set to have no more than five subject enrollment difference between the TAG and the control site.

As such, 82 percent of the surgical controls had their procedures between January of 1998 and May of 2001. The historical and concurrent groups were as such very similar in all major demographic and clinical variables. The primary safety hypothesis that was tested in this pivotal study was that the percentage of subjects with more than one major adverse event through one-year post-treatment will be lower than the TAG device group when compared to the surgical control group.

The primary efficacy hypothesis was that the percentage of subjects, three from major device-related events through one-year follow-up for the TAG device group will exceed 80 percent. The secondary

hypotheses were also tested and they were the procedural blood loss, ICU and hospital stay as well as the time period to return to normal activities will be lower in the TAG device group compared to the surgical control group.

The term major as used in this trial was derived from the Sacks criteria published in 1997 and these were the only criteria available for classification at the time. A major adverse event was one that required therapy and post-hospitalization between 24 and 48 hours or required major therapy and unplanned increase in level of care or prolonged hospitalization resulted in permanent adverse sequelae or death.

A minor adverse event is one that requires no therapy and is of no consequence or requires nominal therapy and is of no consequence, including an overnight admission for observation. For the two separate adverse events to be tracked in the study, were PDP classified and are shown here in these two slides. To illustrate, a paraplegia resulting in permanent deficit or a groin psuedoaneurysm requiring

repair would be classified as major adverse events in this trial, while a transient mental status change not prolonging hospitalization or a small groin hematoma and not requiring treatment would be classified as a minor adverse event.

The sample size estimate for the pivotal trial was based on the primary safety endpoint, which was the one year incidence of major adverse events. Allowing for a Type I error rate of 0.05 (two-sided) and a power of 0.8, the controlled incidence of major adverse events was estimated at 40 percent and the test incidents of major adverse events was estimated at 20 percent. This resulted in a sample size of 82 in both groups for comparison.

Allowing for two training cases per side and subject attrition due to loss to follow-up intent-to-treat failures and deaths, 140 test subjects were enrolled and treated with the TAG device and compared to the 94 controlled patients that were treated by open surgery, 44 were enrolled concurrently with a TAG and the 50 historical patients enrolled by the consecutive review of the most recent surgical

patients in reverse chronological orders at the same institutions.

Key inclusion criteria for all patients in this trial included a descending thoracic aneurysm that necessitated surgical repair, defined as a fusiform aneurysm twice the size of the healthy aorta or any size saccular aneurysm. All patients have to have a life expectancy of more than two years, be surgical candidates and be aged more than 21 years. Exclusion criteria for all patients from this study were mycotic aneurysm and uncontained aneurysmal rupture, all patients with aortic dissections, both acute and chronic, were excluded.

We did not allow planned concomitant surgery or major surgery within 30 days of treatment, MI or stroke within six weeks of treatment, renal insufficiency and degenerative connective tissue disorders. Specific inclusion criteria for the TAG patients, obviously, required in aortic morphology that meets the IFU guidelines, namely aortic diameters between 23 and 37 millimeter and at least 2 centimeter healthy proximal and distal necks.

Specific exclusion criteria for the TAG patients include the patients that have a different size aorta above and below the aneurysm and the inability to compensate for that taper with multiple devices. Patients with significant thrombus of the proximal or distal landing zones, a planned occlusion of the left carotid or the celiac artery and respiratory insufficiency precluding thoracotomy.

Pre-operatively the patients underwent the standard physical examinations, blood tests and medical assessment. Additional imaging including an angiogram and CT scan. Angiography with a marker catheter was used to assess the length of the neck and the length of the aorta to be covered, the location of the aneurysm and the tortuosity associated with it, as well as the axis vessels required to reach that area.

The CT scan was used to get the size and the quality of the proximal neck, the size of the aneurysm, as well as to assess the distal size of the neck and the quality of the aorta at that level. The device was usually inserted through a small groin incision with a contralateral puncture for the

angiographic catheter used in the deployment sequence to assess the exact location of the graft.

The procedure usually started with angiography followed by positioning of the graft to the desired location and concluded with a post-deployment angiography to ensure complete exclusion of the aneurysm. All surgical patients underwent the standard left thoracotomy and standard aneurysmorrhaphy.

Post-procedure, the patient had a full view chest X-ray with views specially designed to show the endograft at discharge. A follow-up schedule was at one month with a CT scan, then at 6 months, 12 months and yearly thereafter with both a chest X-ray and CT scan. This is an example of some of the views that are required to evaluate the graft, and the CT scan was used for the evaluation of endoleaks and the size of the aneurysmal sac over time.

The baseline demographics were very well-matched between both groups. The TAG device group was three years older than the surgical controls, but this was not significant. Of note is that the TAG device

group and the surgical controls were very well-matched when it comes to gender, which is different than the previous trials that enrolled in the abdominal area. This is of particular importance as the aneurysms of the descending thoracic aorta do not show the same predilection to males as the abdominal aorta does.

Baseline aortic morphology was again well-matched between both groups, except for the smaller diameter of the proximal and distal necks in the TAG device, which is expected because of the requirements for sealing.

Of most importance is the aneurysm diameter, which is one of the most important predictors of rupture, as well as an independent predictor of major adverse events. The aneurysm diameter was very well-matched between both groups.

The baseline comorbidities were also quite similar between the TAG device and the surgical control group. Although coronary artery disease appeared to be more prevalent among the TAG device group, this difference was not significant. Symptomatic aneurysms, however, were significantly

more prevalent in the surgical control groups compared to the TAG device.

The risk classifications of the patients in this trial was carried out based on the standard ASA classification and the SVS risk score, and there was no significant difference in either classifications. Both groups had the same risk classification.

There was, however, an imbalance at baseline for the New York Heart Association classification. This particular classification was used mostly to exclude patients with a New York Heart Class IV, which was an exclusion criterion in the study. The large number of patients who did not have classification noted makes the comparison in this category very difficult.

In all, 140 patients underwent the TAG device group in the pivotal trial. 137 of them or 98 percent had a successful implantation of the device. All three failures were due to poor iliac access. 77 patients or 55 percent required more than one device to bridge the aneurysm. 21 patients or 15 percent

required an iliac conduit to the aortic iliac segment to access the aorta. This is an example of the most commonly performed conduit, which is a 10 millimeter Dacron graft to the common iliac artery through a small flank incision.

Operative results that are quite important to surgeons practicing in this field are presented here in the standard reporting format for the surgical area, which is 30 days or in-hospital event rate even after 30 days if the patient stayed in the hospital. If you use this formula, operative mortality is 2 percent for the TAG device and 6 percent for the surgical control. Paraplegia was 3 percent in the TAG device and 14 percent in the control and stroke were both 4 percent in both groups.

The primary safety endpoint in this trial was the percentage of subjects free from major adverse events through one year of follow-up, and the results show a marked reduction in the major adverse events in the TAG device group compared to the surgical control group that was highly significant. 42 percent of the TAG device patients had any major adverse event

through one year while 77 percent of the surgical control group had major adverse events over the first year.

This therapeutic benefit was evident in the following categories. Both bleeding and pulmonary showed a significant reduction of the major adverse events compared to the surgical control group, and this was due to a high percentage of procedural bleeding in the surgical control group and the respiratory failure in the post-operative period.

Renal and wound complications also showed a significantly lower proportion in the TAG device group compared to the surgical control. Of particular note, the neurologic complications in the TAG device group were lower than the surgical control group. Although the patients who had cardiac events was lower in the TAG device group, this was not significant.

The only category that showed a higher major adverse event rate in the TAG device group was that of vascular events, and this was related to the large sheath that was required for the introduction of the device through the iliac system. 11 percent of

those were due to vascular trauma.

The Kaplan-Meier estimates of the freedom from major adverse event over one year shows a substantial advantage to the TAG device group over the surgical controls that is highly significant through the first year. Actually, a 61 percent reduction of these major adverse events is evident by the first 14 days due to the high event rates in the surgical arm periprocedurally.

Of note is that 70 percent of all major adverse events noted in the first year in the TAG device group occurred in the first 30 days. This was also noticed previously in the 97-01 trial where 63 percent of all events over five years actually were noticed in the first 30 days.

Carried all the way through two years, you can see that the benefit to the TAG device group remains significant. All-cause mortality through two years was no different between the TAG device group and the surgical control group. The TAG device group over two years had 24 percent of the patients succumb and in the surgical control group, it was 26 percent.

The causes of death are typical for this elderly population with the associated comorbidities.

Although there is an early numerical advantage to the TAG device group that is associated with the early mortality from the surgical procedure, the freedom from all-cause death through two years is no different for the two arms of the study.

Included in this all-cause mortality is the more relevant aneurysm-related mortality, which is defined as the death prior to hospital discharge or death within 30 days of the primary procedure or any secondary procedure to treat the original aneurysm, which also includes death from ruptures.

Freedom from aneurysm-related mortality through two years was 97 percent for the TAG device group and 90 percent for the open surgical controls. This difference is significant. And as you can note from the graph, there were no mortalities in either arm after the first year that was related to the aneurysm.

In summary, the primary safety endpoint of this pivotal study was met with a significantly lower

proportion of TAG subjects experiencing major adverse events through one year of follow-up. It was 42 percent in the TAG group and 77 percent in the open surgical group.

The primary efficacy endpoint of this pivotal study was the percentage of subjects that were free from major device-related events through one-year follow-up for the TAG device group. The efficacy for the surgical procedure was assumed to be 100 percent. A predefined point estimate of 80 percent for the endovascular group was considered to be a reasonable efficacy outcome and since the device was expected to show a considerable improvement in safety profile.

The major category in the device-related events through one year was again derived from the Sacks criteria and included for the device-related events, endoleaks, migration and realignment, aneurysm enlargement, branch vessel occlusion, deployment failure, extrusion erosion, lumen obstruction and material failure.

To illustrate the definition, endoleaks requiring intervention, such as an additional device,

will be classified as a major device-related event. However, endoleaks not requiring any intervention and being observed by serial imaging will be classified as minor device-related events.

Since endoleaks are the most frequent device-related events in most of these trials, they were further classified according to the same classification for the abdominal aneurysms. Type I was due to either proximal or distal attachment sites. Type II was due to retrograde flow from branches, Type III from a structural defect or junctional endoleak and Type IV from material porosity.

Freedom from major device-related events in this trial over one year was 94 percent for the TAG device. This freedom from major device-related events was significant when compared to the predefined limit of 80 percent. There were eight major device-related events during the first year.

Since 10 patients did not have their 12 month follow-up visit, a worst case analysis was performed assigning a major device-related event to all 10. If that is carried out, the freedom from

major device-related events drops to 87 percent, but even at that level, the lower 95 percent confidence interval is 80.4 percent.

The freedom from major device-related events carried through two years show a stable line after the initial six months without additional major device-related events, especially during the second year. It continues to be 94 percent both at one and at two years and both are significant compared to the 80 percent predefined limit.

So in summary, the primary efficacy endpoint of this pivotal trial was also met with 94 percent of the test subjects free from a major device-related event through one year. This was statistically greater than the predefined limit of 80 percent. In addition, there were no aneurysm ruptures noted through these two years.

Secondary outcomes are reported here by the median value. Procedural blood loss was 250 ml in the TAG device group and 1,850 in the surgical controls. No p-value was reported because of the large number of missing data from the surgical

control. ICU stay was one day for the TAG device and three for the surgical controls, and the hospital stay was three days for the TAG device group and 10 for the surgical control. Time to return to normal activities was reduced to 30 days in the TAG device compared to 78 days for the surgical control.

To summarize the pivotal trial, the TAG device was safe and effective for the treatment of aneurysms of the descending thoracic aorta. The primary safety endpoint was met with 42 percent of the TAG device group having major adverse events and 77 percent for the surgical controls. The primary efficacy endpoint was also met with 94 percent freedom from major device-related events. Both were highly significant. All secondary endpoints were met.

Despite these excellent results, the sponsor chose not to seek approval of the device to the dismay and chagrin of most of the investigators. They decided to proceed with a modification of the device to eliminate the failure mode that was identified in the longitudinal spine fractures.

Mr. Nilson has already discussed with you

the preclinical testing that showed the device to be at least the same or better in most of the bench testing that were performed. A confirmatory study was initiated after the modification to ensure that the early deployment and early results are satisfactory as the spine had some function in the deployment of the device.

The confirmatory study was started in 2003 and finished enrollment in June of 2004 and, again, it was conducted to confirm the functional performance of the modified TAG device during deployment and through the first 30 days. A 30 day endpoint was chosen based on the TAG 99-01 Study, which showed that 70 percent of the major adverse events occurred within the first 30 days in the periprocedural period. That difference was also maintained from 30 days all the way through two years.

The study was carried out at 11 sites. All but one participated in the TAG 99-01 pivotal trial. It was designed as, obviously, a non-randomized prospective trial, all test subjects treated with the modified TAG device, and they were

compared to the control data from the pivotal study, the TAG 99-01. 30 day study endpoints were used, although all patients are planned to have a follow-up of five years.

Identical inclusion and exclusion criteria were used in this study compared to the pivotal study to allow the comparison to the control data from the pivotal trial. The primary safety endpoint for this study was the percentage of subjects with more than one major adverse event through 30 days post-treatment in the TAG device group compared to the surgical control group from the TAG 99-01 Study.

The efficacy endpoint was the percentage of subjects with major device-related events in the TAG device group through 30 days of follow-up. These same secondary endpoints were used for this as the 99-01 and included the procedural blood loss, ICU and hospital stay and the time to return to normal activities.

The sample size estimate for the confirmatory study was again based on the primary safety endpoint, which was the 30 day incidence of

major adverse events allowing for a 5 point error rate of 0.05 and the power of 0.86. The controlled incidence of major adverse events was assumed to be 63 percent and the expected incidence of the TAG device in major adverse events was 38 percent. This led to an estimate of a sample size of 40 requiring the new modified TAG device to be compared to the 94 patients that were in the control arm of the 99-01.

Again, allowing for some subject attrition, 51 patients were enrolled in this study and treated with the modified TAG device and they were compared with the same 94 control subjects that were derived from the TAG 99-01 Study.

The preoperative assessment was very similar to the 99-01 Study, including physical examination, blood test and imaging. The follow-up at discharge, again, included the chest X-ray and at the 30 day follow-up visit, both a chest X-ray and a CT scan were included. All the subjects will continue, obviously, to be followed up through the next five years.

Baseline demographics were, again, quite

similar between the TAG device group and the surgical control group. There were some more male patients in the TAG device group in the 03-03, but this difference was not significant.

Baseline aortic morphology was, again, very similar to the 99-01 Study with well-matched groups between the TAG device and the surgical controls with the only difference being the smaller size of the proximal neck diameter and the distal neck diameter in the TAG device group because of the anatomic requirement of the procedure.

The aneurysm diameter was quite similar between the TAG device and the surgical control group. Baseline comorbidities were also well-matched between the TAG device group and the surgical control arm. In this comparison, the symptomatic aneurysm difference did not reach statistical significance. However, there were more prevalence of cancer or a history of cancer in the TAG device group compared to the surgical control.

Risk classification according to the ASA was very well-matched between the TAG and the surgical

control. The SVS risk score was slightly higher in the TAG device group and this was significant. Again, for the New York Heart Association, there was a large number of patients that were not classified and in this particular case did not reach significance.

The safety endpoints through 30 days again were quite striking showing a significant advantage to the TAG device group compared to the surgical control, major adverse events were noted in 12 percent of the patients treated with the TAG device and 70 percent of the surgical controls. With several categories showing this therapeutic benefit of the TAG device over the surgical controls, including bleeding, pulmonary, cardiac, renal, and again neurologic complications.

The difference in major adverse events between the two groups was significant. Vascular complications were again noted in more patients with the TAG device group compared to the surgical control group and this difference in this particular case was not significant. The freedom from the major device -- from major adverse event through 30 days showed a

significant advantage to the TAG device group compared to the surgical controlled with the P being less than 0.001.

Most of the advantage is noted very procedurally in the very early post-operative period. This slide illustrates all three groups and both trials showing that both the TAG device group from both studies delivered some therapeutic benefit compared to the surgical control.

In summary, the primary safety endpoint of this trial was met with significantly lower proportion of TAG device subjects experiencing major adverse events through 30 days compared to the TAG 99-01 surgical control. There were no TAG device deaths through 30 days. The efficacy endpoint of this confirmatory study was the freedom from major device-related events through 30 days post-treatment. And since no patient experienced a major device-related event in the confirmatory study, the efficacy was 100 percent. The lower 95 percent confidence interval was 93 percent.

In other worst case scenarios, analysis

was performed assigning major device-related events to the two patients that did not complete a 30 day follow-up and this reduced the efficacy to 96 percent with a lower 95 percent confidence interval of 86 percent. The secondary outcomes measured in this confirmatory study are reported as a medium value. The procedural blood loss was 200 ml in the TAG device group and 1850 in the surgical control.

The ICU stay was again one day in the TAG device and three days in the surgical control. The hospital stay was three days for the TAG device and 10 in the surgical control and again the time to return to normal activities was shortened in the TAG device group to 15 days versus 78 for the surgical control.

In summary, the confirmatory study confirms the result of the peak in testing, that the modified design is equivalent or improved over the original design with the primary safety endpoint met, 12 percent TAG versus 70 percent major adverse events in the surgical control with the difference being highly significant and the primary efficacy endpoint being 100 percent freedom from major device-related

events.

In conclusion, the studies of the TAG device show that for treatment of aneurysms of the descending thoracic aorta the TAG device is safer than open surgical repair. It provides effective treatment for aneurysms of the descending thoracic aorta and results in less blood loss, shorter hospital and ICU stay and a quicker return to normal activities compared to the open surgical repair.

Now, I yield the podium to Dr. Mitchell, who will discuss with you the risks and benefits of the TAG device.

DR. MITCHELL: Thank you, Dr. Makaroun. As we have seen, the open repair of descending aneurysms incur significant morbidity and mortality, specifically 6 percent mortality in our series and a 77 percent cumulative morbidity. Compared to the open procedure, the TAG device was able to dramatically lower 30 day mortality from 6 to 1 percent and total morbidity from 77 to 42 percent with a reduction in paraplegia from 14 percent to 3 percent and major pulmonary complications from 38 to 13 percent.

These translate into significantly better patient outcomes and recovery. However, when we consider endovascular repairs, we do introduce some new risks which are specific to endovascular repair and they are listed here. There are possibilities for deployment failure, branch vessel occlusion can occur from inadvertent coverage. There is the new possibility of injury to access vessels. We now have a new problem called endoleaks and aneurysms can enlarge afterwards, devices can migrate and there are instances of material failure.

However, as we've seen in this experience, the incidence of these events has all been relatively low. Less than 4 percent for the greatest problem and ranging around 1 percent for most of these complications. And additionally, most of these complications can be taken care of with subsequent endovascular procedures. The modifications to the TAG device eliminate the risk associated with fractures of the deployment wire and its mechanical and deployment properties have been extensively confirmed by mechanical testing, as well as by the TAG 03